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Prospective Adjuvant Therapy With Mitomycin C and Carmofur (HCFU) for Colorectal Cancer, 10-Year Follow-Up: Tokai HCFU Study Group, the First Study for Colorectal Cancer

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A joint study was performed by the Tokai HCFU study group, which included 41 institutions to study the usefulness of the concomitant therapy with Mitomycin C (MMC) and Carmofur (HCFU) as a postoperative adjuvant chemotherapy in patients with colorectal cancer who had curative resection. Patients were divided into two groups, Group MMC and Group MMC+HCFU, using the "envelope" method. Among the 172 patients who had the envelope opened, 149 evaluable cases were analyzed for evaluation of the drug. The cumulative 10-year survival rates of Group MMC+HCFU had a statistically significant increase in survival rate compared with Group MMC. In particular, the rate was statistically significant in patients with colorectal cancer who had lymph node invasion. There were no severe side effects due to the adjuvant chemotherapy with MMC+HCFU. Thus the adjuvant chemotherapy with MMC+HCFU is suggested to be a useful and safe postoperative adjuvant chemotherapy.

KEY WORDS: **adjuvant chemotherapy, colorectal cancer, MMC, Carmofur**

INTRODUCTION

Recently, the incidence of colorectal cancer in Japan has been increasing. However, the prognosis of patients with colorectal cancer who have a curative resection is prolonged because of the progress of diagnostic technology, e.g., early diagnosis and operative therapy, compared with other digestive cancers. However, colorectal cancer cannot be controlled by operative therapy alone, and appropriate postoperative therapy is required.

1-Hexylcarbamoyl-5-fluorouracil (Carmofur, HCFU, Mifurol) is a 5-FU derivative oral anticancer drug developed by Hoshi et al. [1] and Koyama et al. [2]. Reports of the results of the Phase II study, in which the drug was effective in the treatment of colorectal cancer, have not yet been seen with the 5-FU or its other derivatives. Thus a randomized comparative controlled study on the efficacy of the MMC therapy in combination with HCFU was performed by 41 institutes of the Tokai study group on the adjuvant chemotherapy with MMC+HCFU in Tokai district.

In a previous report [3], we described the 5-year survival rate, asymptomatic rate, and style of recurrence in colorectal cancer followed up for 5 years. Another 5 years have lapsed since the publication of the first report; therefore, this report covers the analyzed results of the cumulative 10-year postoperative survival rates.

MATERIALS AND METHODS

Patients who had a colorectal operation at 41 clinical centers in Tokai district during 2 years (from July 1, 1981 to June 30, 1983) were enrolled in study. Patient eligibility

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TABLE I. Selection of the Cases for Survival Study of Colorectal Cancer

	Arm A	Arm B	Total
Entered cases	79	93	172
Excluded cases	5	7	12 (7.0%)
Eligible cases	74	86	160 (93.0%)
Withdrawn cases	5	6	11 (6.4%)
Evaluable cases	69	80	149 (86.6%)

was assessed as follows: having a colorectal cancer, age <75 years, no severe complication, macroscopically curative resection at the time of operation, no history of any other cancer concomitantly or at a different time. Eligible patients were assigned randomly to one of two treatment groups using the "envelop" method in order of operations performed.

Drug dosage was as follows. Arm A (Group MMC): 2–4 mg of the MMC was given eight times for 4 weeks with one shot IV injection starting the day of the operation. The standard dose was >16 mg of MMC for 4 weeks. Arm B (Group MMC + HCFU): In addition to the same dosage as Arm A, 600 mg of Carmofur (HCFU) was given during a period of >3 months within a year, i.e., the total 54.0 g of the drug was given in divided doses.

The collected case reports were examined at Nagoya University, 2nd Surgery. Case reports were judged by the evaluation committee. The analytical method was based on the "survival rates computing rules according to the Japan Society for Cancer Therapy." Survival rates were computed and analyzed using SAS life test procedures. The uniformity of the background factors was examined by using χ^2-test and U-test. Survival rates were estimated by the Kaplan-Meier method. The generalized Wilcoxon test and the log-rank test were used in analysis of survival rates. In addition, patients who died from other diseases or unknown causes after the identification of recurrence of colorectal cancer and died from unknown causes were treated as "death from colorectal cancer."

RESULTS

A total of 172 patients in 41 institutions were enrolled in the study (Arm A: 79, Arm B: 93). Of the 172 patients, 12 had unsuitable data for efficacy analysis (i.e., over the age: 1, early cancer: 1, overlapping cancer: 2, noncurative resection: 7, severe complication: 1) (Arm A: 5, Arm B: 7). Eleven of the enrolled patients (6.4%, Arm A: 5, Arm B: 6) were put in "incomplete" due to protocol violation. Thus, 149 of the enrolled patients (86.6%) were eligible and completed the study and were analyzed (Arm A: 69; colon cancer: 43, rectal cancer: 26; Arm B: 80, colon cancer: 45, rectal cancer: 35) (Table I). Figures 1 and 2 showed the survival curves of the eligible 160 cases including "incomplete cases" and of 149 evaluable complete cases, respectively. Crude data are shown in Table II.

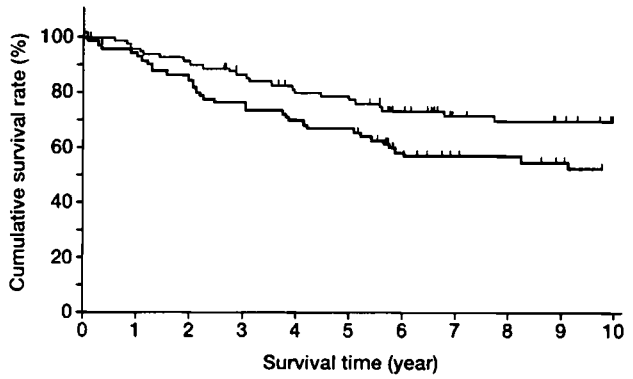

Fig. 1. Eligible cases of colorectal cancer (n = 160); —— Arm A: n = 74, 52.5%; —— Arm B: n = 86, 70.2%; log-rank test: $P = 0.0314$; g-Wilcoxon test: $P = 0.0372$. The 10-year survival rate of arm A (n = 74) was 52.5% and that of arm B (n = 86) was 70.2%, and increased survival rate was found with the statistical difference.

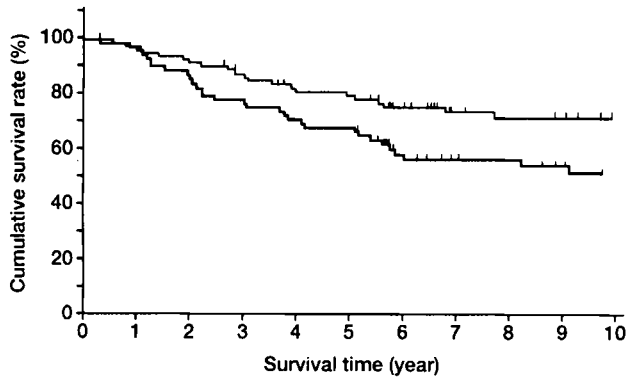

Fig. 2. Evaluable cases (completely eligible) of colorectal cancer (n = 149); —— Arm A: n = 69, 51.7%; —— Arm B: n = 80, 71.7%; log-rank test: $P = 0.0205$; g-Wilcoxon test: $P = 0.0284$. The 10-year survival rate of arm A (n = 69) was 51.7% and that of arm B (n = 80) was 71.7% and increased survival rate was found with the statistical difference.

There were no statistically significant differences between the two arms in terms of the various background factors related to patient survival rates (Table III). The background factors included age and sex as the host factors; tumor size, tumor location, macroscopical, and histopathological depth of tumor (Borrmann's classification), lymph node metastasis and stage, gross appearance classification of tumor, histological type of tumor, lymph node invasion, and vascular invasion as the carcinoma factors. Drug administration to the eligible patients was 16 mg of MMC (standard dosage) given to 91.3% of the patients in Arm A and 87.5% of the patients in Arm B. There was no difference between the two arms; 54.0 g of HCFU (standard dosage) was given to 72.5% of the patients in Arm B (Table IV).

TABLE II. Clinical Background Factors and Follow-Up Data of Colorectal Cancer

		A	B
Host factor			
Age	–40	4	6
	41–50	13	15
	51–60	20	30
	61–70	33	31
	71–75	9	11
Sex	Male	39	50
	Female	40	43
Tumor factor			
Size	–1.9cm	1	0
	2.0cm–3.9cm	18	18
	4.0cm–7.9cm	50	62
	8.0cm–	9	13
	Benign tumor	1	0
Tumor location			
	Colon	46	53
	Rectum	31	40
	Colon and rectum	1	0
	Benign tumor	1	0
Borrmann's classification			
	Type 0	0	1
	Type 1	13	10
	Type 2	51	58
	Type 3	12	19
	Type 4	0	0
	Type 5	0	2
	Benign tumor	1	0
	Not available	2	3
Lymph node metast.: macro			
	$N(-)$	26	34
	$N_1(+)$	30	28
	$N_2(+)$	17	25
	$N_3(+)$	2	3
	$N_4(+)$	3	1
	Benign tumor	1	0
	Not available	0	2
Lymph node metast.: micro			
	$n(-)$	41	58
	$n_1(+)$	25	10
	$n_2(+)$	8	17
	$n_3(+)$	1	3
	$n_4(+)$	0	0
	Benign tumor	1	0
	Not available	3	5
Serosal involvement: macro			
Mucosa		1	0
Submucosa		3	1
Muscularis propria		6	6
Subserosa		16	19
Serosa		42	44
Invasion adjacent structures		9	18
Benign tumor		1	0
Not available		1	5
Serosal involvement: micro			
Mucosa		0	0
Serosal involvement: micro (*contd.*)			
Submucosa		1	1
Muscularis propria		10	12
Subserosa		32	27
Serosa		19	35
Invasion adjacent structures		9	11
Benign tumor		1	0
Not available		7	7
Lymphatic spread:			
	ly_0	17	33
	ly_1	45	42
	ly_2	0	0
	ly_3	0	0
	Benign tumor	1	0
	Not available	16	18
Vascular spread:			
	v_0	37	48
	v_1	14	10
	v_2	1	3
	v_3	0	2
	Benign tumor	1	0
	Not available	26	30
Clinical stage macro:			
	Stage 1	8	4
	Stage 2	15	26
	Stage 3	32	31
	Stage 4	20	27
	Stage 5	3	5
	Benign tumor	1	0
Clinical stage micro:			
	Stage 1	9	8
	Stage 2	25	46
	Stage 3	27	13
	Stage 4	7	14
	Stage 5	1	3
	Benign tumor	1	0
	Not available	9	9
Type of histology			
Well-differentiated adenocarcinoma		41	39
Moderately differentiated adenocarcinoma		32	40
Poorly differentiated adenocarcinoma		2	4
Mucinous carcinoma		1	4
Signet-ring cell carcinoma		0	1
Benign tumor		1	0
Not available		2	5
Follow-up data			
	Alive	27	41
	Lost to follow-up	15	19
	Death of cancer	29	28
	Death from other causes	1	5
	Death	7	0

For the cumulative survival rates, the increase in survival rates was found to be statistically significant (Arm A: 52.5%, Arm B: 70.2%) (log-rank test: $P = 0.0314$, g-Wilcoxon test: $P = 0.0372$) (Fig. 1). Regarding completely eligible patients, the increase in survival rates was found to be statistically significant (Arm A: 51.7%, Arm

TABLE III. Comparison of Clinical Background Factors Between Arm A and Arm B of Colorectal Cancer

	χ^2-test	U-test
Host factor: Age	—	NS (P = 0.088)
Sex	NS (P = 0.488)	—
Tumor factor: Size	—	NS (P = 0.154)
Location	NS (P = 0.996)	—
Borrmann's classification	NS (P = 0.967)	—
Lymph node metast.: N	—	NS (P = 0.859)
: n	—	NS (P = 0.616)
Serosal involvement: S	—	NS (P = 0.357)
: s	—	NS (P = 0.242)
Lymphatic spread: ly	—	NS (P = 0.445)
Vascular spread: v	—	NS (P = 0.674)
Clinical stage: Stage	—	NS (P = 0.891)
: stage	—	NS (P = 0.341)
Type of histology	NS (P = 0.996)	—

NS: not significant.

TABLE IV. Distribution of Patients of Colorectal Cancer in Each Arm by Some Ranges of MMC and HCFU Doses

MMC doses			HCFU doses		
Total doses (mg)	Arm A	Arm B	Total doses (g)	Arm A	Arm B
– 15.9	6	10	– 53.9	—	22
16.0 – 31.9	15	10	54.0 – 218.9	—	30
32.0 –	48	60	220.0 –	—	28

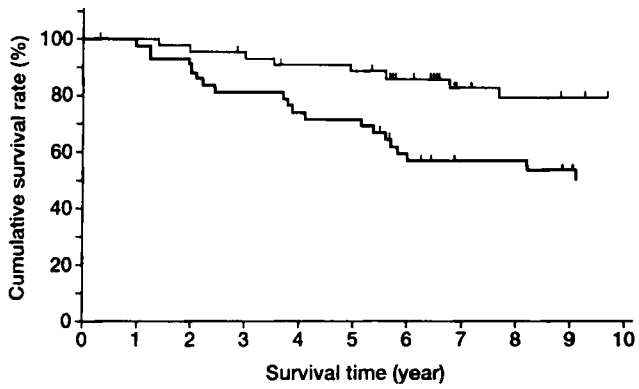

Fig. 3. Eligible cases of colon cancer (n = 88); —— Arm A: n = 43, 49.8%; —— Arm B: n = 45, 79.3%; log-rank test: P = 0.0046; g-Wilcoxon test: P = 0.0049. The 10-year survival rate of arm A (n = 43) was 49.8% and that of arm B (n = 45) was 79.3%, and increased survival rate was found with the statistical difference.

B: 71.7%) (log-rank test: P = 0.0205, g-Wilcoxon test: P = 0.00284) (Fig. 2). For various factors, the increase in survival rates of colon cancer was found to be statistically significant (Arm A: 49.8%, Arm B: 79.3%) (log-rank test: P = 0.0046, g-Wilcoxon test: P = 0.0049) (Fig. 3). Increases in survival rates of patients with rectal cancer in Arm B were found, but the difference was not statistically significant. As for other factors, a marked difference in lymph node invasion was found between Arm A and Arm B (Arm A: 44.3%, Arm B: 74.4%) (log-rank test: P = 0.0046, g-Wilcoxon test: P = 0.0049).

Side effects due to MMC were reported by 27 patients (34.2%) of Arm A and 27 patients (29.0%) of Arm B. Side effects due to HCFU appeared in 23 patients (24.7%) of Arm B (Table V). Main side effects due to MMC were digestive symptoms (such as anorexia, nausea and vomiting, and diarrhea) and leucopenia. Four patients in Arm A and three patients in Arm B were withdrawn because of side effects. Side effects due to HCFU were mainly diarrhea, pollakisuria, general fatigue, nausea/vomiting, and leucopenia. Eight patients were withdrawn, but there was no severe side effects.

The above noted side effects may include those prolonged side effects that occurred during MMC therapy before this study.

DISCUSSION

After the establishment of standard operation methods for the radical resection of colorectal cancer, many controlled studies, mainly in the United States, have been conducted looking at postoperative adjuvant chemotherapy. Results of the studies, however, have not been satisfactory [4–6]. In 1990, Moertel et al. [7] showed the efficacy of therapy with levamisole plus 5-FU, which

TABLE V. Toxicity of MMC and HCFU in Adjuvant Chemotherapy of Colorectal Cancer

	MMC[a]		HCFU[b]
	Arm A[c]	Arm B[d]	Arm B
Entered cases	79	93	93
Cases without toxicity	52 (65.8%)	66 (71.0%)	70 (75.3%)
Cases with toxicity	27 (34.2%)	27 (29.0%)	23 (24.7%)
General fatigue	13 (16.5%)	12 (12.9%)	3 (3.2%)
Anorexia	11 (13.9%)	13 (14.0%)	1 (1.1%)
Nausea or vomiting	7 (8.9%)	4 (4.3%)	3 (3.2%)
Diarrhea	7 (8.9%)	8 (8.6%)	8 (8.6%)
Leucopenia	10 (12.7%)	3 (3.2%)	3 (3.2%)
Hot sensation	0 (—)	0 (—)	1 (1.1%)
Pollakisuria	0 (—)	0 (—)	5 (5.4%)
Others	5 (—)	5 (5.4%)	5 (5.4%)

[a]Total standard dose was >16 mg for 4 weeks.
[b]Total standard dose was 54.0 gm for 3 months
[c]2–4 mg of MMC was given 8 times for 4 weeks, one shot IV, starting the day of the operation.
[d]In addition of the same dosage as Arm A, 600 mg of HCFU per day was given for >3 months.

was determined to be a standard therapy for colorectal cancer by the FDA. The efficacy of this postoperative adjuvant chemotherapy has been reconsidered, and additional studies have been conducted. Although the controlled study with MMC performed by the Imanaga Group belongs to the Ministry of Health and Welfare in Japan, satisfactory results were not obtained because of questions about the statistical analysis [8].

Accordingly, using the intermittent administration of moderate doses of MMC in addition to the prolonged oral HCFU, which was the combination therapy used by Imanaga Group, a joint study concerning whether or not it produces good results for the "distant result" was conducted. Recently, survival periods after recurrence have been prolonged because of aggressive surgical liver resection for the liver metastasis of colorectal cancer [9]. Therefore, the evaluation period for survival rates in patients with colorectal cancer should be 10 years, since a 5-year follow-up may not be sufficient. Some of the clinical centers in which the operations were performed could not follow up for 10 years. Therefore, "asymptomatic period" and "style of recurrence" could not be examined in some patients, and they were treated as "death from unknown causes," i.e., "death due to carcinoma."

1-Hexylcarbamoyl-5-fluorouracil(Carmofur, HCFU, Mifurol) is a masked compound developed in Japan as an oral anticancer drug of 5-FU group. The results of the phase II study conducted by Koyama et al. [2] showed a 43.3% efficacy (of the 30 patients, CR: 1, PR: 12). Thus the drug was considered to be the best anticancer drug in the 5-FU group. The results of the studies by Morioka et al. [10] and Niimoto et al. [11] showed the same effectiveness as our study for colorectal cancer.

The cumulative 6-year survival rates were 45.2% for Arm A and 73.1% for Arm B (statistically significantly, $P = 0.045$, g-Wilcoxon test). However, since the previously described report, many patients have withdrawn and many patients died within the 5 years since their operation in Arm A; the previous report was only an interim report. The cumulative 10-year survival rates recognized an increase in the number of deaths in the 5th and 6th year after the operation. Four patients with metastatic lung cancer were recognized both in Arm A and Arm B. These were considered to be the late recurrence of colorectal cancer.

The survival rates classified by locations in the patients with colon cancer in Arm B were significantly higher than Arm A, whereas there was no significant difference between the two arms in the patients with rectal cancer. Recurrence in patients with colon cancer [12] were liver metastasis in six patients in Arm A and three in Arm B, and lung metastasis in four patients in Arm A and one in Arm B. It is thought that the prolongation of life was attained by the prevention of colon cancer recurrence due to hematogenous metastasis. HCFU has no preventive effect on the hematogenous metastasis in the patients with rectal cancer. It is not known if differences occurred between colon and rectal cancer, and these are problems to be investigated.

As for the survival rate classified by clinical background factors, especially in the patients with lymph node invasion and histological lymph node metastasis, significant results were obtained in Arm B compared to Arm A (log-rank test: $P < 0.05$, g-Wilcoxon test: $P < 0.05$). In addition, the difference in the uniformity of clinical background factors between Arm A and Arm B was equally significant in spite of these stratifications. It is well known that HCFU is easy to transport into the lymph, compared with other drugs of the 5-FU group [13]. Although the lymph node metastasis in the control (Group MMC) was not a high ratio, patients with lymph node invasion and with historogical lymph node metastasis are

at high risk. HCFU is thought to be very effective in these high risk patients.

Side effects due to HCFU occurred in 24.7% of the patients. However, these side effects may be due to MMC, which was given just before the administration of HCFU. The incidence of the side effects that occurred during the phase II study was <39.1%. Symptoms of the side effects were mainly gastrointestinal disturbances, but also included sensations of pollakisuria, characteristic of HCFU. Cumulative toxicity due to long-term administration of HCFU was not found.

As noted, concomitant treatment with MMC and HCFU is useful for patients with colorectal cancer who had a curative resection. We are now conducting a randomized comparative controlled study on the efficacy of HCFU single dosage for those with colorectal cancer who had a curative resection, compared to the control group, patients who had only a curative resection. According to the interim report, the 5-year asymptomatic ratio was statistically significant compared to the control group [14]. In the future, the usefulness of HCFU will be confirmed by cumulating the data on the postoperative adjuvant chemotherapy for patients with colorectal cancer.

CONCLUSIONS

A randomized comparative controlled study was conducted at 41 clinical centers in Tokai district in order to study the concomitant efficacy of MMC plus HCFU as a postoperative adjuvant chemotherapy in the patient with colorectal cancer who had a curative resection, and the following results were obtained.

1. Adjuvant chemotherapy with MMC plus HCFU increased significantly the 10-year survival rates in patients with colorectal cancer who had a curative resection (log-rank test: $P = 0.0314$, g-Wilcoxon test: $P = 0.0372$).
2. In the patients with colon cancer and lymph node invasion, a significant increase in survival rates was recognized (log-rank test: $P < 0.005$, g-Wilcoxon test: $P < 0.05$).
3. Side effects of HCFU occurred in 23 patients (24.7%). The main side effects were diarrhea, pollakisuria, general fatigue, nausea/vomiting, and leucopenia. No severe adverse events occurred.

From these results, concomitant therapy with MMC plus HCFU is thought to be a useful and safe postoperative adjuvant chemotherapy for the patient with colorectal cancer who had a curative operation.

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